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Clinical Implications of Genetic Defects in G Proteins: Oncogenic Mutations in $G\alpha_s$ as the Molecular Basis for the McCune-Albright Syndrome

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Signal-transducing guanine nucleotide-binding proteins (G proteins) couple extracellular receptor proteins to intracellular effector enzymes and ion channels, and therefore are critical mediators of cellular responses to external stimuli. G proteins are comprised of three subunits (α, β, γ), each encoded by many different genes. The multiplicity of G protein subunits facilitates great combinatorial variability, which, in part, accounts for the ability of G proteins to interact with many different receptor and effector proteins. Hundreds of G protein-coupled receptors have been identified, and their unique patterns of expression among a restricted number of cell types contributes greatly to the apparent specificity of hormone action. Mutations that either activate or inactivate some of these receptors account for a number of highly specific syndromes, which affect a limited number of target tissues. By contrast, most G proteins are widely expressed in many tissues. Accordingly, mutations in these signaling molecules would be expected to produce a more generalized pattern of hormone dysfunction. Activating mutations in the gene (GNAS1) that encode the α subunit of the G protein that stimulates adenylyl cyclase (AC) have been identified in many endocrine neoplasms and diverse tissues of patients with McCune-Albright syndrome. The McCune-Albright syndrome is characterized by autonomous endocrine function, hyperpigmented skin lesions, and fibrous dysplasia of bone—effects which reflect the ability of CAMP to stimulate cell function and proliferation in a wide variety of tissues. The unusual features of the McCune-Albright syndrome are explained by the mosaic distribution of cells bearing the mutant allele, an observation that is most consistent with postzygotic mutation of GNAS1. Experimental analysis of this syndrome has extended our understanding of the clinical and biochemical consequences of dysfunctional G protein action and has provided a bench-to-bedside demonstration of the critical role that G proteins play in transmembrane signal transduction in humans. © 2000 IMSS. Published by Elsevier Science Inc.

Key Words: G proteins, Cyclic AMP, Neoplasia, McCune-Albright syndrome.

Introduction

Signal-transducing guanine nucleotide-binding proteins (G proteins) couple extracellular receptor proteins to intracellular effector enzymes and ion channels, and therefore are critical mediators of cellular responses to external stimuli. G proteins are heterotrimers comprised of three subunits (α, β, and γ), each encoded by a family of different genes. Different combinations of these G protein subunits allow for great diversity in the composition of the heterotrimers. This, in part, accounts for the ability of G proteins to interact specifically with different receptor and effector proteins. The G protein-coupled receptors have a common serpentine structure, which consists of seven membrane-spanning alpha helices and detects extracellular signals as diverse as light photons, odorants, hormones, growth factors, and neurotransmitters (1). G proteins regulate activity of many second messenger systems, including enzymes such as adenylyl cyclase (AC), phospholipase C, and phospholipase A_2, and ion channels.

The critical role that G proteins play in regulating cellular responses to extracellular signals implies that altered G protein expression or activity can have significant biological consequences (2). Germline and somatic mutations of

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the human GNAS1 gene located at 20q13.11 (3,4), which encodes the α subunit of the G protein (G_s) that stimulates adenylyl cyclase (AC), have been identified as the basis for several clinical disorders. Characterization of many of these naturally occurring mutations has provided substantial insight into functional domains of $G\alpha_s$, and in many instances has complemented or confirmed analyses of mutant α chains developed in the research laboratory (5). For example, early laboratory studies indicated that replacement of either arginine[201] or glutamine[227] of $G\alpha_s$ inhibits the intrinsic GTPase activity, resulting in constitutive activation of AC and increased production of cAMP (6,8). Subsequent human genetic analyses revealed that somatic mutations in the GNAS1 gene that replaced these two key amino acids were present in a subset of *GH* (GH)-secreting pituitary and thyroid adenomas (9,10). Similar mutations have also been found in patients with the McCune-Albright syndrome (MAS), a sporadic disorder characterized by increased hormone production and/or cellular proliferation of many tissues (11,12). By contrast, heterozygous germline mutations of the GNAS1 gene that decrease expression or function of $G\alpha_s$ are present in subjects with Albright hereditary osteodystrophy (AHO), an autosomal dominant disorder associated with a constellation of developmental defects including obesity, short stature, brachydactyly, and subcutaneous ossification (13). Most patients with AHO also show reduced responsiveness to multiple hormones (14–18), a condition termed pseudohypoparathyroidism (PHP) type 1a. These hormones, which include parathyroid hormone (PTH), thyroid stimulating hormone (TSH), and glucagon, bind to receptors that require $G\alpha_s$ to trigger activation of AC. By contrast, other patients with AHO appear to have normal hormonal responsiveness in spite of identical loss-of-function GNAS1 mutations, a condition termed pseudopseudohypoparathyroidism (13).

MAS and AHO represent contrasting gain-of-function and loss-of-function mutations in the same gene. Experimental analysis of these two syndromes has extended our understanding of the clinical consequences of dysfunctional G protein action, and has provided unexpected insights into the importance of cAMP as a regulator of the growth and/or function of many tissues. This review will focus on the biology of activating mutations of GNAS1, from bench to bedside, as a paradigm for many of the clinical implications of altered G protein function.

G Protein Structure and Function

G proteins share a common heterotrimeric structure consisting of an α subunit and a tightly coupled βγ dimer. The α subunit interacts with detector and effector molecules, binds GTP, and possesses intrinsic GTPase activity (19). Mammals have over 20 different G protein α chains encoded by 16 genes; additional protein diversity results from the generation of alternatively spliced mRNAs. The various G protein α chains can be grouped into four major classes (G_s, G_i, G_q, and G_{12}) according to structural and functional homologies. The GTP-liganded α chain is the primary regulator of membrane-bound ion channels and enzymes that generate intracellular second messengers. The α subunits associate with a smaller group of β ($\geq$5) and γ ($>$12) subunits (20). The β and γ subunits combine preferentially with one another (21,22) and the resultant βγ dimers demonstrate specific associations with different α subunits (23,24). Combinatorial specificity in the associations among various G protein subunits provides the potential for enormous diversity, and may allow distinct heterotrimers to interact selectively with only a limited number of the more than 1,000 G protein-coupled receptors (25,26). At present, it is unknown whether specific G protein subunit associations occur randomly or whether there are regulated mechanisms that determine the subunit composition of heterotrimers.

The binding and hydrolysis of GTP regulate the activity of G proteins (Figure 1). In the basal (nonstimulated) state, G proteins exist in the heterotrimeric form, with GDP tightly bound to the α chain. Upon receptor activation, a conformational change occurs in the α chain, which facilitates the exchange of bound GDP for GTP, with subsequent dissociation of the α-GTP chain from the βγ dimer and the receptor. The free α-GTP chain is able to interact with effector enzymes and ion channels to regulate their activity. In addition, free βγ dimers can also participate in downstream signaling events (27,28). For example, βγ dimers can influence activity of certain forms of AC and phospholipase C, open potassium channels (29), participate in receptor desensitization (30,31), mediate mitogen-activated protein (MAP) kinase phosphorylation (32,33), and modulate leukocyte chemotaxis (34). The interaction of α-GTP with the effector molecule is terminated by the hydrolysis of GTP to GDP by an endogenous GTPase. The GTPase reaction is a high-energy transition state that requires association of the γ-phosphorous atom with the oxygen of a water molecule. To catalyze this reaction, the γ-phosphate of GTP must be stabilized so that a straight line, perpendicular to the plane of the γ-phosphate, connects the water, γ-phosphorous, and oxygen molecule, leaving the β-phosphate. The precise arrangement of these atoms is maintained through interaction with key amino-acid residues, which have been identified through x-ray crystallography and *in vitro* mutagenesis experiments (35–46). These studies indicate that arginine[201] and glutamine[227] in $G\alpha_s$ function as fingers to stabilize the γ-phosphate of GTP. With hydrolysis of GTP to GDP, the α-GDP chain reassociates with the βγ dimer and the heterotrimeric G protein is ready for another cycle of receptor activation.

The intrinsic GTPase of each Gα chain provides a molecular switch that controls the intensity of the signaling event. Accordingly, structural alterations of Gα chains that slow GTP hydrolysis will delay termination of the signal transduction process and cause persistent and excessive signaling.

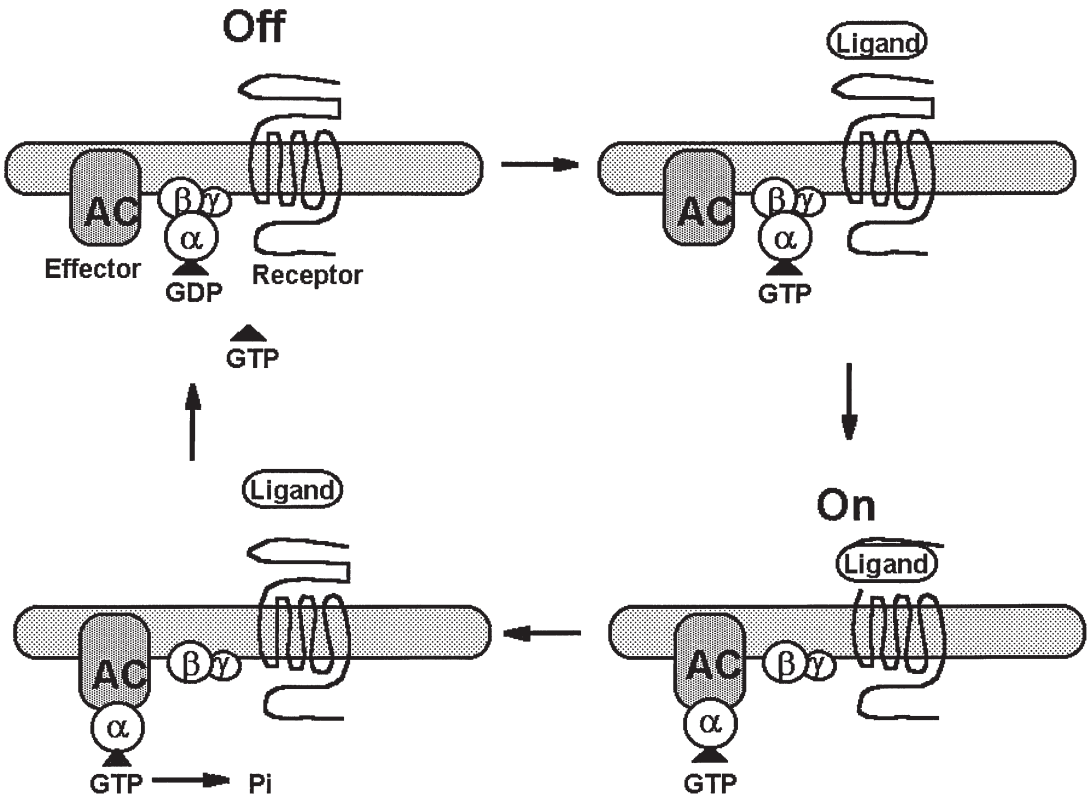

Figure 1. The G protein GTPase regulatory cycle. In the nonstimulated, basal (Off) state, GDP is tightly bound to the α chain of the heterotrimeric G protein. Binding of an agonist (Ligand) to its receptor (depicted with seven transmembrane spanning domains) induces a conformational change in the receptor, and enables it to activate the G protein. The G protein now releases GDP and binds GTP present in the cytosol. Binding of GTP to the α chain leads to dissociation of the α-GTP from the βγ dimer, and each of these molecules is now free to regulate downstream effector proteins. Hydrolysis of GTP to GDP by intrinsic GTPase of the α chain promotes reassociation of α-GDP with βγ and the inactive state is restored. The heterotrimeric G protein is ready for another cycle of hormone-induced activation.

G Protein Regulation of AC

Many hormones and growth factors regulate cell growth and proliferation through their ability to bind and activate receptors that are coupled by G proteins to various isoforms of AC (47). In many cell types, intracellular cAMP is not only a potent mitogenic signal but is also an important stimulus for hormone production and/or secretion. Activity of AC is under dual regulatory control through receptors that interact with either G_s to stimulate AC or with G_i to inhibit AC (48). Additional complexity in the control of AC activity derives from the observation that several forms of AC are also regulated by protein kinase C–signaling pathways through the intercession of still other G proteins (49,50). Thus, AC acts as a coincidence detector, and its activity is determined by a complex and coordinate interplay between multiple G protein subunits and other regulators (e.g., calcium-calmodulin) (25,51).

Activating Mutations of the GNAS1 Gene

The critical role that cAMP plays in stimulating the growth and proliferation of many cell types makes mutations in this signaling pathway likely candidates as the basis for several endocrine diseases (52). Indeed, a growing number of inherited and sporadic endocrine disorders has now been attributed to either germline or somatic mutations in $G\alpha_s$ or to its receptors, which produce constitutive (i.e., hormone-independent) activation of AC (2,53). Vallar et al. (54) initially described a subset of human GH-secreting pituitary tumors that exhibited increased AC activity *in vitro* in the absence of added GH-releasing hormone. The molecular basis for constitutive activation of AC in these somatotropic tumors was subsequently identified as an oncogenic form of $G\alpha_s$ termed *gsp*, which lacked GTPase activity due to the replacement of either arginine[201] or glutamine[227](9,10). These mutations enable the $G\alpha_s$ subunit to remain in the active GTP-bound state, and thereby cause persistent and excessive synthesis of cAMP in affected cells. Such activating mutations occur in approximately 40% of somatotropic tumors (Table 1) and may distinguish a subset of tumors more sensitive to inhibition of *GH* secretion by somatostatin analogs (55,56). In addition to *GH*-secreting pituitary tumors, *gsp* mutations are also present in a small number of AC thyroid hormone (TH)-secreting pituitary tumors (55,57), a subset of thyroid neoplasms, and testicular and ovarian stro-

mal Leydig tumors (58), but are rare in other endocrine tumors (Table 1). Moreover, *gsp* mutations have been described in ovarian cysts that cause isosexual gonadotropin-independent precocious puberty (59,60) and in isolated fibrous dysplasia of the bone (61).

The amino acids arginine^{201} and glutamine^{227} are located in domains of $G\alpha_s$, which are required for GDP/GTP binding and intrinsic GTPase activation (62–66). Modification of these key amino acids can have profound consequences. For example, the exotoxin secreted by *Vibrio cholerae* catalyzes the addition of an ADP-ribose moiety to the side chain of arginine^{201} in $G\alpha_s$. This covalent modification markedly reduces GTP hydrolysis, maintaining $G\alpha_s$ in its active GTP-bound form, and causing ligand-independent stimulation of AC (67). The subsequent accumulation of cAMP in intestinal epithelial cells stimulates secretion of salt and water into the intestine and produces, in part, the watery diarrhea associated with cholera.

Amino acid glutamine^{227} corresponds to the cognate amino acid, Gln^{61}, in the low molecular weight (LMW) GTP-binding protein p21^{ras}. Replacement of this amino acid inhibits the protein's intrinsic GTPase, leading to constitutive activation of signaling pathways transforming *in vitro* (68,70). Naturally occurring Gln^{61} mutations convert p21^{ras} into an oncogene present in a variety of human tumors (71).

Molecular Basis for the McCune-Albright Syndrome

First described in 1937, the McCune-Albright syndrome (MAS) (27,73) is a sporadic syndrome characterized by the clinical triad of polyostotic fibrous dysplasia, café-au-lait skin lesions, and endocrine hyperfunction. The unusual distribution of skin and bone lesions in MAS and the development of excessive endocrine function in the absence of stimulatory or tropic hormones is explained by the presence of *gsp* mutations in affected tissues of patients with this syndrome (11,12). GNAS1 mutations that lead to the replacement of arginine^{201} [e.g., Arg^{201}(CGT)→His(CAT) or Cys(TGT)] have been identified in DNA isolated from tissues of patients with MAS (11,12,74–77); surprisingly, similar mutations that replace the nearby glutamine at position 227 have not been described.

Table 1. Clinical syndromes associated with activating mutations of GNAS1*

McCune-Albright Syndrome	(100%)
Pituitary adenomas	(4–50%)
Growth hormone-secreting adenomas	(35–40%)
ACTH-secreting adenomas	(4–9%)
Clinically non-functioning adenomas	(rare)
Thyroid neoplasms	(3–70%)
Hyperfunctioning and nonfunctioning follicular adenomas	
Papillary and follicular carcinomas	
Parathyroid neoplasms	(<5%)
Parathyroid adenomas	
Adrenocortical disorders	(<5%)
Aldosterone-producing adenomas	
Adrenal hyperplasia	
Pheochromocytoma	
Leydig cell and ovarian neoplasms	(66%)

ACTH = adrenocorticotropin.

*For further information please refer to Reference 99.

The *gsp* mutation is not present in all tissues of patients with MAS. Cells containing a GNAS1 gene mutation are distributed in a mosaic pattern, the greatest number of *gsp*-containing cells present in the most abnormal areas of affected tissues (Figure 2) (11,12,75,78,79). These molecular observations confirmed the hypothesis, initially proposed on the basis of clinical observations, that the variable involvement of endocrine organs and eccentric distribution of skeletal and skin lesions represents mosaicism, which is derived from a postzygotic somatic mutation (80). Similarly, the lack of documented heritability of MAS has been interpreted as evidence that germline transmission of the mutation would be lethal (80).

The variable involvement of different tissues in patients with MAS likely reflects several biological effects. First, the *gsp* mutation arises early in embryogenesis and therefore affects cells that are then distributed in a mosaic pattern. The proportion and distribution of affected cells in a tissue will be determined by the precise stage of development at which the mutation occurred. Thus, mutational events that occur later in embryogenesis are likely to give rise to fewer mutant cells and a milder phenotype than mutational events that occur very early. As a corollary, acquisition of a *gsp* mutation months or even years after birth could explain the development of a solitary endocrine tumor or a single fibrous dysplasia lesion in some patients. A second determinant of clinical phenotype is based on the variable ability of cAMP to induce proliferation in different cells. Thus, mutational activation of $G\alpha_s$ will have the most significant consequences in tissues, in which cAMP stimulates cellular proliferation and/or hormone secretion. Cyclic AMP is not mitogenic in all cell types and, in some, cAMP can actually inhibit growth. Even in cells where cAMP is a strong growth stimulator, changes in the expression of other genes (56) or induction of counter-regulatory responses (such as increased cAMP phosphodiesterase activity 881–85) could mitigate or even reverse the effects of the activated $G\alpha_s$ phenotype. Finally, the impact of the *gsp* mutation may be further diminished on the basis of the reduced half-life of activated $G\alpha_s$ molecules (86–88).

It is unknown whether endocrine, skin, and skeletal lesions in MAS patients represent the proliferation of mosaic rests of cells harboring the *gsp* mutation, or whether they result from the acquisition of additional gene mutations. Based on the variable impact of *gsp* mutation in different tissues, a second genetic hit may be required for proliferation or excess hormone secretion in some tissues (89–91). However, in other cells, such as melanocytes (92–94) or somatotropes (85,95), persistently elevated levels of cAMP may be sufficient to alter cellular phenotype.

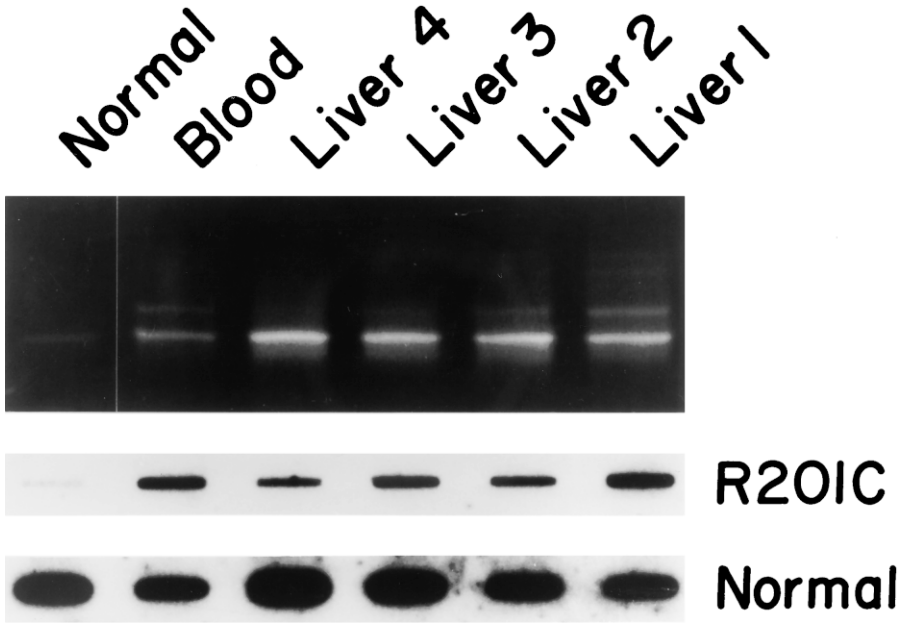

Figure 2. Analysis of PCR-amplified fragments spanning exon 8 of the GNAS1 gene. Genomic DNA was isolated from peripheral blood leukocytes from a Normal subject (first lane) and from a patient with MAS, including peripheral blood leukocytes (Blood) and four distinct regions of the liver (Liver 1–4) obtained at the time of liver transplant. This patient had hepatitis and cirrhosis, and each region of the liver showed a different degree of destruction. The upper panel shows analysis after denaturing gradient gel electrophoresis. Normal DNA shows only a single homoduplex band corresponding to wild-type sequence for exon 8, whereas all DNA samples from the patient showed an additional, more slowly migrating band that corresponded to sequence of exon 8 in which Arg^{201} was replaced by Cys (R201C). The lower panels show autoradiograms representing hybridization of the PCR products with radioactive oligonucleotides specific for either the mutant allele (R201C) or the wild-type allele (Normal). The R201 allele is present to varying degrees in all DNA samples obtained from the patient with MAS. The percentage of mutant alleles (expressed as mutant divided by total) ranged from 10% in the blood to 25% in Liver 1, with 50% indicating that all cells contain the mutant allele.

Not surprisingly, cells bearing the *gsp* mutation are also present in tissues not usually affected in MAS (Figure 2), including peripheral blood leukocytes, liver, heart, thymus, and the gastrointestinal tract (11,12,96). In some tissues, such as the parathyroids, *gsp* mutation may have little effect, because chronically elevated levels of intracellular cAMP seem to play a limited role in parathyroid cell proliferation or hormone secretion (97). On the other hand, the presence of *gsp* mutation in other tissues has, in some patients, been associated with clinical consequences such as hepatitis, cardiac arrhythmias, or intestinal polyps. Recently, a more severe form of MAS was described, in which patients manifest jaundice, hepatitis, extramedullary hematopoiesis, gastrointestinal polyps, thymic hyperplasia, acute pancreatitis, neurodevelopmental disorders, and even sudden cardiac death (96,98). This severe phenotype may result from a very early somatic mutation, resulting in the distribution of large numbers of affected cells throughout the body. Remarkably, this phenotype demonstrates the wide variety of cell types that can be influenced by G_s-coupled signaling pathways, and in which excessive cAMP can produce profound consequences.

Clinical Manifestations of McCune-Albright Syndrome

We previously reviewed the literature in English by Medline search (1966–1996) and cross-referencing (1926–1996), and identified 158 reported cases of MAS (99). Clinical data are summarized below and in Table 2. The reader is referred to Reference 99 for a more comprehensive discussion of the findings.

Polyostotic fibrous dysplasia (PFD). Solitary or multiple expansile fibrous dysplasia lesions are present in nearly all (98%) patients with MAS. These lesions typically develop during the first decade of life (Table 2) and can cause progressive deformity, fractures, and nerve entrapment. The femur and pelvis are most commonly involved. Radiographs of affected bones reveal expansile, lytic lesions with a ground-glass pattern, and a scalloped border secondary to endosteal erosion. Bone histology discloses three primary but distinct histological patterns: (1) Chinese writing type, (2) sclerotic/pagetoid type, and (3) sclerotic/hypercellular type, characteristically associated with the axial/appendicular skeleton, cranial bones, or gnathic bones, respectively (100). These lesions bear only faint resemblance to those found in hyperparathyroidism (osteitis fibrosa cystica) and, with rare exceptions (101,102), PTH levels are typically normal in patients with MAS. Solitary lesions (mono-ostotic fibrous dysplasia) are present in a minority of patients with MAS.

The basis for the unusual cellular changes in fibrous dysplasia is poorly understood. Recent evidence indicates that the fibrotic areas consist, in fact, of an excess of cells with

Table 2. Clinical characteristics of patients with the McCune-Albright syndrome

	Patients (n = 158)	Male (n = 53)	Female (n = 105)	Age at diagnosis (years)	Comments
Fibrous dysplasia	154	51	103	7.7 (0→52)	Polyostotic more common than mono-ostotic
Café-au-lait lesions	135	49	86	7.7 (0→52)	Variable size and number of lesions, irregular border (Coast of Maine)
Precocious puberty	82	8	74	4.9 (0.3→9)	Common initial manifestation
Acromegaly/Gigantism	42	20	22	14.8 (0.2→42)	17/26 with adenoma on MRI/CT
Hyperprolactinemia	23	9	14	16.0 (0.2→42)	23/42 of acromegalics with ↑ PRL
Hyperthyroidism	30	7	23	14.4 (0.5→37)	Euthyroid goiter is common
Hypercortisolism	9	4	5	4.4 (0.2→17)	All primary adrenal
Myxomas	8	3	5	34 (17→50)	Extremity myxomas
Osteosarcoma	3	1	2	36 (34→37)	At sites of fibrous dysplasia, not related to prior radiation therapy
Rickets/Osteomalacia	4	1	3	27.3 (8→52)	Responsive to phosphorous plus calcitriol
Cardiac abnormalities	17	8	9	(0.1→66)	Arrhythmias and CHF reported
Hepatic abnormalities	16	6	10	1.9 (0.3→4)	Neonatal iciterus is most common

CT = computer tomography, MRI = magnetic resonance imaging, PRL = prolactin, CHF = congestive heart failure.

phenotypic features of pre-osteogenic cells, whereas the lesional bone formed *de novo* within fibrotic areas represents the biosynthetic output of mature but abnormal osteoblasts. It is likely that at least some of the phenotypic changes in affected osteogenic cells result from cAMP-induced increases in expression of interleukin-6 and the c-fos proto-oncogene (76,103–106). The mosaic distribution of lesions in fibrous dysplasia may also play an important pathogenic role, as close contact between transplanted normal bone cells and osteogenic cells containing the *gsp* mutation is necessary to reproduce the fibrous dysplasia lesion in mice (107).

PFD also occurs in patients who lack other features of MAS, and similar *gsp* mutations have been identified in these isolated lesions (76,108).

Although no treatment appears entirely satisfactory, preliminary studies have demonstrated that pamidronate, a powerful bisphosphonate that can inhibit bone resorption, is at least partially effective in treating fibrous dysplasia bone lesions (105,109).

Café-au-lait skin lesions. Patients with MAS typically have one or more pigmented macules, termed café-au-lait lesions, that have irregular borders, termed Coast of Maine. By contrast, café-au-lait skin lesions that occur in patients with neurofibromatosis (Von Recklinghausen's syndrome) have a smooth border (Coast of California). Distribution of skin lesions in MAS is also characteristic: lesions rarely extend beyond the midline, and the majority tend to be on the same side of the body as the skeletal lesions. They occur most commonly on the buttocks and lumbo-sacral regions.

Endocrine abnormalities. Endocrine disorders are common in MAS and are characterized by autonomous and excessive function of hormone-producing tissues (Table 2). Serum concentrations of tropic or stimulating hormones are typically normal or reduced. The most common endocrine disorder is gonadal hyperfunction. Precocious pseudopuberty, characterized by abnormally elevated sex hormones with low or undetectable serum levels of gonadotropins, has been reported in over 60% of patients with MAS (99). Precocious puberty is a common initial manifestation of MAS in girls, and characteristically presents as thelarche and/or vaginal bleeding in a girl under 5 years of age. Typically, estrogen levels are elevated as a result of ovarian cysts, and serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are low. Sex hormone secretion is typically unassociated with follicular maturation or ovulation, and patients lack reproductive ability. Some girls have regular menses and rapid pubertal development, whereas others have irregular or intermittent bleeding associated with relatively normal rates of growth. Estrogen production appears related to the growth and involution of small ovarian cysts, and ovarian activity can undergo spontaneous remission in some cases. Large, benign ovarian cysts may also occur (59,60), and surgical excision may result in regression of secondary sexual characteristics until onset of normal pubertal development. Patients typically have low or suppressed levels of serum LH and FSH, which fail to increase significantly after administration of gonadotropin-releasing hormone (GnRH), a characteristic of gonadotropin-independent precocious puberty (i.e., precocious pseudopuberty). Testing may be normal during intervals of apparent ovarian inactivity, however. It is interesting that, after several years of excessive sex steroid exposure, some girls experience a transition to central precocious puberty, particularly those with bone age of 11 years or older (110,111). As adults, women with a past history of gonadotropin-independent precocious puberty are generally fertile, although they may have occasional irregular menses due to continued autonomous production of estrogen.

Treatment of girls with MAS and precocious puberty is problematic. Therapy with GnRH analogs and super-agonists is not effective unless there has been a progression to central precocious puberty (111). Treatment with the aromatase inhibitor testolactone (110,112), or more recently, with ketaconazole (113), has been successful for short periods of time, but long-term therapy has generally been disappointing.

Pituitary-independent precocious puberty also occurs in boys with MAS, but is much less common than in young girls. Approximately 10% of reported MAS patients with precocious puberty are male. Testicular biopsy in these cases reveals variable degrees of seminiferous tube development and Leydig cell hyperplasia. Treatment is similar to that for familial male precocious puberty, due to activating mutations of the LH receptor (i.e., testitoxicosis) (114–116) and consists of the combination of testolactone plus spironalactone.

GH excess and/or hyperprolactinemia are common in patients with MAS, and many patients have features of acromegaly and galactorrhea. Gigantism in children and adolescents has also been described. The biochemical behavior of GH-producing pituitary tumors in patients with MAS appears indistinguishable from that of sporadic tumors with and without *gsp* mutations. GH secretion is stimulated by TRH, GHRH, and sleep and is incompletely suppressed by glucose administration. However, only 65% of MAS patients with GH excess have radiographic evidence of a pituitary tumor, a much lower incidence than in sporadic cases of acromegaly (99%) (99). In addition, hyperprolactinemia occurs in over 50% of MAS patients with elevated GH levels, a frequency somewhat greater than in patients with sporadic pituitary tumors (40%) (99). Medical therapy with somatostatin analogs and bromocriptine has been shown to reduce tumor size and hormonal secretion in many, but not all, patients (55,56).

Autonomous thyroid nodules and hyperthyroidism have been reported in approximately 33% of MAS patients who underwent thyroid evaluation (99,117). Thyroid nodules have been treated by radioactive iodine ablation or surgery. The degree of hyperthyroidism is variable, and serum concentrations of TSH are typically low. The thyroid gland will often appear normal on physical examination, but nodules are nearly always detectable by sonography. Patients lack clinical or serological evidence of autoimmune thyroid disease and thyroid-stimulating immunoglobulins are undetectable.

Patients with MAS occasionally develop autonomous function of the adrenal gland and primary hypercortisolism at a young age (mean age, 4.4 years) (99). Adrenal gland histopathology reveals either nodular hyperplasia or solitary adenoma.

Hypophosphatemic rickets and osteomalacia can develop in patients with polyostotic fibrous dysplasia, with or without the MAS phenotype. The pathophysiological basis for hypophosphatemia appears to be decreased renal tubular reabsorption of phosphorous, but the cause remains unknown. Two theories have been proposed to explain hyperphosphaturia in MAS: (1) the production of a circulating phosphaturic factor, termed phosphatonin, by fibrous dysplasia lesions and (2) an intrinsic defect in renal tubular reabsorption of phosphate (118). Recent studies suggest that both hypotheses are plausible. Activating mutations of $G\alpha_s$ have been identified in the kidneys of patients with MAS, and could result in excess generation of cAMP in proximal tubular cells and consequent reduction in tubular reabsorption of phosphorous. Indeed, basal levels of nephrogenous cAMP are elevated in some MAS patients with hypophosphatemia, in spite of normal serum levels of PTH (118). However, these observations cannot exclude the possibility that a circulating phosphaturic factor is also present in MAS patients with hypophosphatemia. Occurrence of hypophosphatemic osteomalacia in patients with isolated fibrous dysplasia supports the notion that similar bone lesions in patients with MAS may elaborate a phosphaturic factor.

Conclusions

Activating and inactivating mutations in the gene encoding $G\alpha_s$ are now known to be the basis for two well-described contrasting clinical disorders—MAS and AHO. The identification of somatic mutations in the GNAS1 gene in patients with MAS has yielded the molecular basis for many features of this unusual disorder, and provides important insights into the role of cAMP in controlling cellular proliferation and hormone secretion in many cell types. Further investigation will be necessary, however, to determine the identity and contributions of the other genes that modify the phenotypic expression of the *gsp* mutation.

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